Research/Recherche

Adverse reactions to sulfa drugs: implications for malaria chemotherapy

A. Björkman[1] & P.A. Phillips-Howard[2]

National adverse drug reaction registers in Sweden and the United Kingdom provided data on the type, severity and frequency of reported adverse reactions attributed to sulfa drugs. Reactions to the ten principal drugs were examined in terms of their half-lives and usual indications for use. Of 8339 reactions reported between 1968 and 1988, 1272 (15%) were blood dyscrasias, 3737 (45%) were skin disorders, and 578 (7%) involved the liver. These side-effects occurred with all types of sulfa drugs investigated, although at different relative rates, and 3525 (42%) of them were classified as serious. The overall case fatality rate (CFR) was 1:15 serious reactions, and was highest in patients with white blood cell dyscrasias (1:7). Drugs with longer elimination half-lives had higher CFRs, particularly for fatalities after skin reactions.

In Sweden, the estimated incidences of serious reactions were between 9 and 33 per 100 000 short-term users of sulfa drugs (two weeks), between 53 and 111 among those on malaria prophylaxis, and between 1744 and 2031 in patients on continuous therapy. For dapsone, the incidence appeared to increase with higher doses.

Our results indicate that sulfa drugs with short elimination half-lives deserve to be considered for use in combination with proguanil or chlorproguanil for malaria chemotherapy and possibly prophylaxis. The smaller risk of adverse reactions associated with lower-dose dapsone suggests that it should also be evaluated as a potentially safe alternative.

Introduction

Antimalarial drugs currently available for the prophylaxis and treatment of malaria do not fully satisfy the criteria for effective but safe control. With the increase of drug resistance in *Plasmodium falciparum*, the efficacy of chloroquine and proguanil for prophylaxis of non-immune populations has decreased, and therapy using chloroquine alone has become increasingly unreliable (*1*). Sulfa drugs in synergistic combination with dihydrofolate reductase inhibitors (DHFRI) have been shown to be prophylactically and therapeutically effective (*2*). The one most widely used, sulfadoxine–pyrimethamine (Fansidar), has limited prophylactic application because of the risk of serious adverse reactions (*3, 4*). The case fatality rate from *P. falciparum* infection is, however, considerably higher than the risk of fatality from a serious reaction to sulfadoxine–pyrimethamine when used for therapy. Another compound antimalarial, dapsone–pyrimethamine (Maloprim), has also been widely recommended for prophylaxis. When administered in Sweden as a double dose (dapsone 200 mg weekly) serious reactions were estimated to occur in 1/2000 (*5*). It continues to be used as a single-dose weekly prophylaxis in some countries (*6*). The similar synergistic activity of proguanil with dapsone was first observed in Vietnam in 1973 (*7*). An alternative to this, the combination of dapsone with chlorproguanil, has recently been shown to be effective therapy for *P. falciparum* infections in Kenya (*8*). Both sulfadoxine and dapsone have long elimination

[1] Associate Professor, Department of Infectious Diseases, Roslagstull Hospital, S-114 89 Stockholm, Sweden. Requests for reprints should be sent to this address.

[2] Honorary Lecturer, Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London, England. At present, with the Malaria Unit, Division of Control of Tropical Diseases, World Health Organization, Geneva, Switzerland.

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half-lives—200 hours and 28 hours, respectively. It has been proposed that equally effective, but safer, sulfa drugs would be those with shorter half-lives. Two such drugs, sulfafurazole and sulfamethoxazole, were recently reported to be highly effective in prophylaxis when combined with proguanil (*9, 10*). The frequency of serious reactions, especially fatalities, due to sulfa drugs in relation to their half-lives or duration of use has not, however, been fully elucidated.

It has been common practice to depend on post-marketing surveillance to indicate the incidence of adverse reactions to antimalarial drugs. However, much time is lost while such data accumulate. We have chosen an alternative approach in order to ascertain more rapidly (although crudely) the adverse reactions that could be expected to occur with shorter- and longer-acting sulfa drugs. Adverse reactions attributed to sulfa drugs used as anti-infective agents were investigated, using the national adverse drug reaction registers in Sweden and the United Kingdom. These data were then used to derive some inferences regarding the proposed use of short-acting sulfa drugs combined with proguanil.

Study methods

Drugs investigated

The main sulfa drugs used in Sweden and the United Kingdom during the 1970s and 1980s were investigated. Those that had adverse reactions attributed to them were defined according to their international nonproprietary (INN) and proprietary names, duration of therapy, elimination half-lives, and indications for use (Table 1). The indications for the different drugs were similar in both countries; however, sulfafurazole, sulfisomidine and Sulfapral had only been marketed in Sweden. Similarities were also noted regarding doses and duration of the drug regimens except for dapsone–pyrimethamine (Table 1).

National registers

The Swedish and British national registers were both initiated in the early 1960s and share several similarities. However, reporting in Sweden of serious and new reactions has been compulsory for physicians since 1975 whereas British physicians are encouraged to voluntarily report all reactions to new drugs, and all serious reactions to existing drugs. In both registries, reactions are judged by specialists who assess causality. In the Swedish register, the causal relationship between the reaction and the drug is classified as possible/probable or remote/not assessable.

Reports of adverse reactions

Information on adverse reactions to sulfa drugs was requested from the national registers of Sweden and the United Kingdom. Only those reactions classified as probably or possibly causal are included in this

Table 1: **Principal sulfa drugs used in Sweden and the United Kingdom**

International nonproprietary name	Proprietary name	Total adult dose	Duration of treatment	Mean elimination half-life	Common indication[a]
Sulfafurazole	Gantrisin	6000 mg daily	2 weeks	6 hours	UTI
Sulfisomidine	Elkosin	4000 mg daily	2 weeks	7 hours	UTI
Sulfadiazine	Triminsulfa	820 mg daily	2 weeks	10 hours	UTI
Sulfamethoxazole (+trimethoprim)[b]	Bactrim, Septrin, Eusaprim	1600 mg daily	2 weeks	10 hours	UTI, ARTI
Sulfamethizole Sulfamethoxypyridazine	Sulfapral	1000 mg 400 mg daily	2 weeks	3 hours 40 hours	UTI
Dapsone (+pyrimethamine)	Maloprim	200 mg[c] weekly	5–12 weeks	28 hours	Malaria CP
Sulfadoxine (+pyrimethamine)	Fansidar	500 mg weekly	5–12 weeks	200 hours	Malaria CP/T
Sulfasalazine[d]	Salazopyrin	3000 mg daily	Continuous	10 hours[e]	Crohn's disease, ulcerative colitis
Dapsone	Alvosulfon	100 mg daily	Continuous	28 hours	Dermatitis herpetiformis

[a] UTI: urinary tract infection; ARTI: acute respiratory tract infection; CP: chemoprophylaxis; T: therapy.
[b] Sulfamethoxazole+trimethoprim = co-trimoxazole = Bactrim, Septrin and Eusaprim.
[c] 200 mg weekly in Sweden, predominantly 100 mg in the United Kingdom.
[d] Sulfapyridine and 5-aminosalicylic acid.
[e] 6 hours in fast acetylators and 14 hours in slow acetylators.

paper. The number of reported cases with adverse reactions to sulfa drugs was established by investigating the data routinely recorded on the register print-outs. Information was usually limited to the drug type, the reaction as classified by organ system, and any fatal outcome.

The seriousness of reactions was estimated by ourselves, according to clinical criteria. Thus, 90% of blood dyscrasias were considered to be serious. For cutaneous reactions, only those that were debilitating or life-threatening, e.g., mucocutaneous syndrome and erythema multiforme, were classified as serious, whereas simple rashes and pruritus were considered to be minor since they were transient and did not require medical treatment. Serious adverse reactions were then further subdivided according to the principal organ system, but an additional distinction was made for haematological disorders. These were grouped separately into the three main blood cell components. Because of the importance of serious reactions, each reaction was tabulated separately. Consequently, an individual case could have two to three serious reactions reported. Similarly, more than one reaction may have been attributed to a fatal case. Case fatality rates were estimated for each type of serious reaction.

Estimates of drug users

The incidences of adverse reactions were estimated only for the Swedish data, since figures for usage rates of specific sulfa drugs in the United Kingdom were difficult to obtain for several reasons, the main one being the vast number of different manufacturers.

Total sales figures of drugs since 1972 are available in Sweden, and are expressed as volume (packs or tablets) or "defined daily doses" (DDDs). In addition, the National Corporation of Swedish Pharmacies has maintained, from a random sample of all prescriptions, a continuous registration of patients' ages and sex and the name, amount and dosage of the corresponding drugs. From the number of DDDs and mean duration of use we could estimate the number of users for the drugs. For the malaria prophylactic drugs the estimates were based on total doses/tablets and packs sold and a mean travel period of three weeks (*5, 11*). Allowance was made for a proportion of unused tablets, e.g., for sulfadoxine–pyrimethamine doses carried for self-therapy (packs of three tablets). For the long-term treatment drugs, i.e., sulfasalazine and dapsone alone, estimates were made of the number of new patients per year who initiated treatment with the respective drugs (*12, 13*).

Results

All reported reactions

In total, 8339 reactions were reported and attributed to sulfa drugs in Sweden and the United Kingdom, of which 67% were attributed to drugs within the co-trimoxazole group (i.e., sulfamethoxazole + trimethoprim) (Table 2). Of all these reactions, 15% were blood dyscrasias, 45% were skin lesions, and 7% involved the liver. Except for sulfafurazole (numbers were too small), reactions related to blood, skin or liver were reported for all sulfa drugs, although the relative frequencies differed. For example, with dapsone, 49% of all reactions reported were related to blood and 10% to the skin; whereas with sulfadoxine–pyrimethamine, the corresponding figures were 7% and 34%, respectively.

Serious reactions. A total of 3525 reactions (42% of all the reactions reported) were classified as serious (Table 3). Over 90% of blood dyscrasias were considered serious, compared with 74% of respiratory disorders, 61% of hepatic disorders, and only 12% of skin reactions. There was no clear correlation between the proportion of serious to non-serious reactions reported, and the half-life of the sulfa drug.

Table 2: **Total number of adverse reactions, by organ or system involved, attributed to sulfa drugs in Sweden and the United Kingdom reported to national registers, 1965–88**

Sulfa drug	Total	Blood	Skin	Liver	Cardio-vascular	Respir-atory	Gastro-intestinal	Renal	Musculo-skeletal	Neuro-logical	Psychi-atric	Eye	General	Other
Sulfafurazole	14	4	7	0	0	0	0	0	0	0	0	0	3	0
Sulfisomidine	37	2	28	3	0	0	0	0	0	0	0	0	4	0
Sulfadiazine	231	23	122	4	0	4	16	1	5	4	0	2	46	4
Co-trimoxazole	5624	676	2815	304	90	78	433	53	102	232	120	63	538	120
Sulfapral	614	71	309	95	0	5	6	7	8	1	1	2	107	2
Maloprim	177	51	30	7	14	8	13	0	5	11	2	2	27	7
Fansidar	175	13	59	37	2	13	7	4	3	6	0	3	22	6
Dapsone	155	76	15	22	2	1	5	5	0	11	4	2	4	8
Sulfasalazine	1312	356	352	106	15	39	85	23	22	68	31	11	110	94
Total	8339	1272	3737	578	123	148	565	93	145	333	158	85	861	241

Table 3: **Number of serious reactions, by organ, tissue or system involved, attributed to sulfa drugs in Sweden and the United Kingdom reported to national registers, 1965–88**

Sulfa drug	Total	WBC[a]	RBC[a]	Thrombo-cytes	Skin	Liver	Cardio-vascular	Respir-atory	Gastro-intestinal	Allergy	Fever	Fetal	Other
Sulfafurazole	6	1	1	2	2	0	0	0	0	0	0	0	0
Sulfisomidine	8	1	0	1	2	0	0	0	0	1	3	0	0
Sulfadiazine	103	11	3	8	18	1	0	4	5	1	40	0	12
Co-trimoxazole	2171	330	129	238	270	217	19	54	210	90	345	26[b]	243
Sulfapral	294	37	16	11	83	26	0	5	2	25	78	0	11
Maloprim	68	22	15	2	1	5	4	2	5	1	2	3	6
Fansidar	87	5	3	1	18	22	1	12	1	0	15	1	8
Sulfasalazine	682	228	86	24	48	68	8	31	25	9	64	26[b]	65
Dapsone	103	22	40	3	2	15	1	1	0	0	3	3	13

[a] WBC: white blood cell; RBC: red blood cell. Pancytopenia grouped with both WBC and RBC.
[b] Fetal reactions included a variety of defects and thus did not constitute one specific syndrome.

The relative frequency of different types of serious reactions varied with the drugs. Serious skin disorders were relatively more frequent (20%) with drugs used for a short duration (two weeks) than with drugs used for malaria prophylaxis (12%) or continuous therapy (5%). In contrast, the relative frequencies of white blood cell (WBC) dyscrasias with these drugs were 13%, 17% and 27%, respectively.

Fatalities

There were 236 fatalities attributed to reactions from sulfa drugs (Table 4), over 60% of which were associated with co-trimoxazole, the drug most commonly used. The attributed cause of death (more than one reaction in some cases) varied with the type of drug. Overall, 38% of fatalities were associated with WBC dyscrasias, this reaction being especially common among the fatal cases taking dapsone or dapsone–pyrimethamine (73%) and sulfasalazine (63%). Skin reactions were considered to contribute to 17% of fatalities but all who died from sulfadoxine–pyrimethamine had had skin reactions. Several organ systems were associated with fatalities due to co-trimoxazole; 20% of these were skin lesions. Only 6% of the fatalities had major liver reactions whereas 11% had other gastrointestinal reactions, mainly pseudomembranous colitis.

Case fatality rates. The overall case fatality rate (CFR) was 1:15 serious reactions reported. CFR was generally higher in the United Kingdom (1:11) than in Sweden (1:23). For sulfasalazine and dapsone, the two drugs used for continuous therapy, the CFR were 1:13 and 1:9, respectively. For the other drugs the CFRs varied between 1:52 and 1:10 (Table 5). CFRs were particularly high with WBC dyscrasias, and appeared to be higher for drugs with longer half-lives, i.e., dapsone–pyrimethamine, sulfadoxine–pyrimethamine and Sulfapral (1:6 to 1:3), compared to those with shorter half lives (1:11 to 1:9). CFRs were lower among patients with skin and

Table 4: **Number of deaths from adverse reactions, by organ, tissue or system involved, attributed to sulfa drugs reported to Swedish and British national registers, 1965–88**

Sulfa drug	Total[a]	WBC	RBC	Thrombo-cytes	Skin	Liver	Circulatory	Heart	Respiratory	Gastro-intestinal	Allergy	Renal	Other
Sulfafurazole	0	0	0	0	0	0	0	0	0	0	0	0	0
Sulfisomidine	0	0	0	0	0	0	0	0	0	0	0	0	0
Sulfadiazine	2	1	0	0	0	0	0	0	0	0	1	0	0
Co-trimoxazole	142	35	39	24	28	8	2	1	3	15	3	1	6
Sulfapral	17	6	2	1	4	2	0	0	0	0	1	1	0
Maloprim	7	6	0	1	0	0	0	1	0	0	0	0	0
Fansidar	6	1	0	0	6	2	0	0	0	0	0	0	0
Sulfasalazine	51	34	12	1	2	4	3	1	0	0	0	1	1
Dapsone	11	7	0	0	1	1	0	0	0	0	0	0	2
Total	236	90	53	27	41	17	5	3	3	15	5	3	9

[a] When more than one serious reaction, deaths have been allotted to each possibly fatal reaction manifested; thus, total deaths are less than total reactions. Deaths attributed to pancytopenia are grouped with both WBC and RBC.

Table 5: **Case fatality rates associated with sulfa drugs in Sweden and the United Kingdom, as reported to national registers, 1965–88**

Sulfa drug	Mean elimination half-life (hours)	Case Fatality rates			
		Total	WBC	Skin	Liver
Sulfadiazine	10	1:52	1:11	—[a]	—
Co-trimoxazole	10	1:15	1:9	1:10	1:27
Sulfapral	3 and 40	1:17	1:6	1:21	—
Sulfasalazine	10	1:13	1:7	1:24	1:17
Maloprim	28	1:10	1:4	—	—
Dapsone	28	1:9	1:3	1:2	1:15
Fansidar	200	1:15	1:5	1:3	1:11
Total		1:15	1:7	1:11	1:24
95% C.I.		1:13–17	1:6–9	1:8–16	1:17–36

[a] No death reported.

hepatic reactions, and higher for drugs with longer half-lives. Hence, for sulfadoxine–pyrimethamine, one third of patients with skin reactions died, but only one in ten and one in 21 among patients who took co-trimoxazole and Sulfapral, respectively.

Reported reaction rates in Sweden

Crude estimates of adverse reaction rates to sulfa drugs in Sweden are presented in Table 6. Rates of serious adverse reactions were relatively low with sulfafurazole and sulfisomidine, two drugs used mainly in the 1970s and, to a large extent, by children; 8/14 (57%) reactions with sulfafurazole and 6/27 (22%) reactions with sulfisomidine were seen in children below 10 years of age. For sulfisomidine, half of the sales were in the form of syrup suggesting that at least half of the users were children. Sulfapral, withdrawn from the market after 1982, also had a low rate of reported serious reactions, 8 in 100 000 users. Co-trimoxazole had an overall reported rate of 33 in 100 000 users, which in the 1970s and 1980s was 27 (95% CI, 24.2–29.8) and 45 (95% CI, 41.6–48.4), respectively. For co-trimoxazole, only 7% of doses were sold as syrup and 4% of adverse reaction reports were in the age group 0–9 years.

The drugs used for periods longer than two weeks had significantly higher reported rates of serious reactions, ranging from 78 to 2031 per 100 000 users. The elimination half-lives did not appear to affect the adverse reaction rates within each subgroup of indication for use.

Discussion

The total number of adverse reactions reported from Sweden and the United Kingdom were similar, although the population in the latter is seven times greater. There was a higher case fatality rate in the United Kingdom, probably because voluntary reporting of reactions leads to underreporting of non-fatal reactions. Between 1960 and 1980 the

Table 6: **Crude estimates of adverse drug reaction rates to sulfa drugs per 100 000 users in Sweden**

Drug	Mean duration of medication	Mean elimination half-life (hours)	All reaction rates[a] (per 100 000)	Serious reaction rates (per 100 000)	Fatality rates (per 100 000)	No. of deaths
Sulfafurazole	2 weeks	6	12	6	—	0
Sulfisomidine	2 weeks	7	34	9	—	0
Sulfadiazine	2 weeks	10	32	19	0.4	2
Co-trimoxazole	2 weeks	10	63	33	1.4	39
Sulfapral	2 weeks	3 and 40[b]	13	8	0.4	17
Maloprim	8 weeks	28	167	111	18.9	3
Fansidar	8 weeks	200	90	78	2.8	2
Sulfasalazine	10 years	10	2211	1744	49.8	8
Dapsone	10 years	28	2585	2031	184.6	4

[a] Includes non-serious reactions.
[b] Sulfamethizole (3 hours) and sulfamethoxypyridazine (40 hours).

proportion of all cases of serious blood dyscrasias reported in Sweden increased from 25% to 50% (Wiholm, personal communication, 1990) whereas in the United Kingdom the proportion of all cases reported is estimated to be below 10% (*14*). The large spectrum of adverse reactions recorded were qualitatively similar in the two countries. In addition, all sulfa drugs investigated appeared to cause adverse reactions in the haematological, skin and liver organ systems, but at different absolute rates. However, the relative frequencies of adverse reactions among different drugs and organ systems were similar for both countries.

Comparisons between the drugs may be confounded not only by factors such as dose and duration of use, but also by indications of use, type of population (e.g., age groups, region of travel abroad), and the time period of use as reporting has improved in recent years in both countries. These confounding factors are discussed below.

Doses given varied substantially among the different drugs (Table 1) but the dosage did not seem to be a clear indicator of toxicity. However, for an individual drug, e.g., dapsone–pyrimethamine in the two countries (see below), the doubling of a dose may have a significant effect upon the incidence of adverse reactions.

Duration of drug exposure may be an important determinant of adverse reactions. Indeed, among serious reactions to sulfa drugs, a small cluster occurs within 1–3 days in previously sensitized individuals; then a larger cluster develops after 1–9 weeks (skin disorders and blood dyscrasias) and up to 3 months later (liver disorders) (*11, 15*). Unfortunately, the quality and quantity of data were insufficient to indicate a clear pattern for each drug. However, since late reactions such as WBC dyscrasias were relatively less frequent with drugs used for short periods, it may be assumed that these reactions would become more frequent if such drugs were used over longer periods, e.g., sulfafurazole for malaria chemoprophylaxis. The number of reported adverse reactions to antimalarial drugs may be an underestimate because reactions occurring abroad are not always recorded in the drug register of the traveller's home country (*16*). This may have a bearing on the reporting of early reactions such as skin reactions, which usually occur within two weeks after taking the drug.

We subdivided the reactions into three major groups according to the indication of use: (1) acutely ill patients with short-term use of sulfa drugs against bacterial, mainly urinary tract infections (UTI) but also acute respiratory tract infections (ARTI); (2) healthy subjects taking malaria prophylaxis; and (3) patients with chronic illnesses and continuous intake of sulfa drugs. Patients in the third group, with ulcerative colitis and Crohn's disease, may be considered to be at greater risk of serious adverse reactions. Acute bacterial infections may also possibly affect the incidence of adverse reactions, although drug reactions such as mucocutaneous syndrome are thought to be more related to viral infections (*17*), like those due to EB virus and HIV (*18*), in which there are immunological disturbances. An increased reaction rate in AIDS patients has been reported for co-trimoxazole (*18, 19*) and to a lesser extent for sulfadoxine–pyrimethamine (*20*). The general profiles of the side-effects in AIDS patients were similar to those presented in Table 4. Interestingly, continuation of treatment despite co-trimoxazole hypersensitivity has been shown to be possible (*21*) but rechallenge has also resulted in severe anaphylactoid reaction (*22*).

Another important confounding feature of adverse reactions to sulfa drugs is age. Previous studies have shown increased risk of serious and life-threatening reactions in the elderly (*23*). This was confirmed in our study in the case of sulfisomidine and co-trimoxazole, which suggested that the incidence of serious reactions in children below 10 years was about half that in an older population. We were unable to control for age within the overall analysis. However, since it is the elderly who are predominantly treated with sulfa drugs other than sulfafurazole and sulfisomidine for urinary tract infections, while the majority of non-immunes taking antimalarial prophylaxis for longer periods are healthy young adults, our study would have underestimated rather than overestimated the differential in risk between short- and longer-term use of sulfa drugs.

Reporting of adverse reactions to drugs has improved in recent years, so that fewer were probably reported prior to than during the 1980s. This is confirmed by the approximately 1.6-fold increase in reports per number of users for co-trimoxazole in the 1980s compared to the 1970s. It must be assumed that the reports for sulfafurazole, sulfisomidine and Sulfapral, which were mainly used in the 1970s were underestimated in relation to co-trimoxazole and other drugs by 30–60%.

Our data did not take into account the background incidence of adverse events without the use of sulfa drugs; however, the background incidences for the main serious side-effects are all insignificant when compared with the rates reported. For example, the background incidence of agranulocytosis/aplastic anaemia is below 1 per 100 000 person-years (*24*), whereas the reported incidence of WBC dyscrasia in relation to co-trimoxazole use in Sweden is estimated at 130 per 100 000 person-years as 33 serious reactions occur per 100 000 users with

an average medication period of 2 weeks (Table 6) and 15% of the serious reactions are WBC dyscrasias (Table 3).

The data used to measure the frequencies of adverse reactions to sulfa drugs in Sweden are subject to many biases, and the rates calculated are recognized to be crude estimates. The use of specific sulfa drugs in the United Kingdom was difficult to obtain because of the vast number of different manufacturers and trade names. However, prescription data were available on antimalarial sulfa drugs (*11*). While the rates of serious reactions to sulfadoxine–pyrimethamine in both countries were similar, the use of dapsone–pyrimethamine presented 11 serious disorders per 100 000 users and a fatality rate of 2 per 100 000 in the United Kingdom, which was ten times lower than in Sweden. This tenfold difference may, in part, be due to the doses used (two tablets weekly in Sweden, and one tablet weekly in the United Kingdom for 13 of the 16 years) (*4*). In addition, dose-dependent toxicity would at least partly explain the large difference in rates between dapsone and dapsone–pyrimethamine (Maloprim) (Table 6). The Australian Defence Forces have utilized dapsone–pyrimethamine once weekly for many years with a good safety record (Rieckmann, personal communication, 1990), and are considering weekly (100 mg or less) or daily (8 mg) low-dose dapsone in combination with daily proguanil as a safe alternative regimen.

The CFR was higher among patients who used sulfa drugs with longer elimination half-lives than shorter. This was especially significant for agranulocytosis and the mucocutaneous syndrome (Table 5). Such a difference is not unexpected, because when an individual experiencing early symptoms of a reaction stops taking a long-acting sulfa drug, its effects will continue for a prolonged period. It is also possible that slow acetylators taking drugs with longer elimination half-lives may be more prone to fatal reactions.

The incidence of adverse reactions was higher in patients taking sulfa drugs in combination with pyrimethamine. The role of pyrimethamine in sulfa toxicity is, however, not clear. Trimethoprim only rarely causes side-effects when used alone, mainly in the form of skin reactions and WBC dyscrasias (*25*). However, these did not appear to be increased in patients who used sulfamethoxazole with trimethoprim (co-trimoxazole), compared with those who used sulfa drugs only. On the other hand, for UTIs, the reaction rates were slightly higher with co-trimoxazole than with the other sulfa drugs used alone (Table 6), although this may at least partly be explained by higher rates in the elderly and by better reporting in the 1980s. We cannot therefore exclude the fact that trimethoprim may have contributed to some extent to the reactions seen with co-trimoxazole.

Sulfa drugs are effective against chloroquine-resistant *P. falciparum* only when combined with the DHFRIs. Pang and colleagues (*9*) indicated that the efficacy of sulfafurazole rose from 24% to 95% when combined with proguanil. In a further study, sulfamethoxazole at a dose of 25 mg/kg daily as an alternative short-acting sulfa drug was also effective when combined with progunail (*10*). This combination is appropriate also because both drugs would be given together on a daily basis, and would therefore be less subject to dosing errors.

It is important to note that a fivefold higher risk of adverse events associated with co-trimoxazole compared with sulfafurazole was calculated from the Swedish data. This is, in part, due to increased reports of reactions to co-trimoxazole in the 1980s (sulfafurazole was used mainly in the 1970s); it also reflects the differential age risk since co-trimoxazole users were older than those taking sulfafurazole; it may also, to some degree, be due to the combination with trimethoprim. However, the rate differential may not solely be attributed to these factors, and we suggest that sulfamethoxazole may have a higher risk for all reactions, including severe and fatal events, compared with sulfafurazole.

Proguanil is considered to be a nontoxic and safe antimalarial drug. It may be assumed that this is also true when it is used combined with a sulfa drug. It has been recognized, however, that a proportion of subjects may be poor metabolizers of proguanil and chlorproguanil (*26*). When given one of these two drugs with sulfa, the poor metabolizers would then receive reduced protection but may still remain potentially at risk, even if low, of a toxic reaction. Studies are required to identify the proportion of prophylactic users who may possibly be at such risk.

The relative gains in giving drugs of reduced toxicity and potency are marginal when considering therapy against potentially fatal *P. falciparum* infections. However, the risk with drugs prescribed for presumptive self-therapy must be more carefully considered, since it can be expected that a proportion of users will treat themselves unnecessarily for non-malarious infections (*16*).

All types of adverse reactions have occurred with the use of all the different sulfa drugs; duration and possibly frequency of use appear to be risk factors as well as the total dose. CFRs appear to be significantly higher for drugs with longer elimination half-lives. We suggest that low-dose and shorter-acting, rather than longer-acting, sulfa drugs should be tested for therapeutic and also prophylactic efficacy in a number of epidemiological situations.

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Résumé

Réactions indésirables aux sulfamides: conséquences pour la chimiothérapie du paludisme

Les registres nationaux de pharmacovigilance de Suède et de Grande-Bretagne ont fourni des données sur le type, la gravité et la fréquence des réactions indésirables notifiées, attribuées aux sulfamides. Les réactions aux dix principaux médicaments ont été examinées en fonction de leur demi-vie et de leurs indications habituelles. Sur les 8339 réactions notifiées entre 1968 et 1988, 1272 (15%) étaient des dyscrasies sanguines, 3737 (47%) étaient des affections cutanées, et 578 (7%) concernaient le foie. Ces effets indésirables se sont produits avec tous les types de sulfamides examinés bien qu'avec des fréquences différentes, et 3525 (42%) d'entre elles ont été classées comme graves. Le taux global de létalité (TL) était de 1:15 pour les réactions graves, et était maximal pour les réactions de type dyscrasie sanguine (1:7). Les médicaments à longue demi-vie avaient des TL plus élevés, particulièrement pour les décès après réaction cutanée.

En Suède, les incidences estimées de réactions graves variaient de 9 à 33 pur 100 000 utilisateurs de sulfamides en traitement de courte durée (deux semaines), de 53 à 111 chez les sujets suivant une prophylaxie du paludisme, et de 1744 à 2031 chez des malades en traitement continu. Pour la dapsone, l'incidence paraissait augmenter avec la dose.

Les résultats montrent que l'emploi de sulfamides à courte demi-vie en association avec du proguanil ou du chlorproguanil pourrait être envisagé pour la chimiothérapie du paludisme, et peut-être pour sa prophylaxie. Le moindre risque de réactions indésirables associé aux faibles doses de dapsone laisse à penser que l'emploi de ce médicament pourrait également être évalué comme alternative plus sûre.

References

1. WHO Technical Report Series, No. 805, 1990 (*Practical chemotherapy of malaria*: report of a WHO Scientific Group).
2. **Peters, W.** *Chemotherapy and drug resistance in malaria.* London and New York, Academic Press, 1987.
3. **Peto, T.E.A. & Gilks, C.F.** *Lancet*, **1**: 1256–1260 (1986).
4. **Phillips-Howard, P.A. & Björkman, A.** *Bulletin of the World Health Organization*, **68**: 493–504 (1990).
5. **Friman, G. et al.** *British medical journal*, **286**: 1244–1245 (1983).
6. **Bradley, D.J. & Phillips-Howard, P.A.** *British medical journal*, **299**: 1087–1089 (1989).
7. **Black, R.H.** *Medical journal of Australia*, **1**: 1265–1270 (1976).
8. **Watkins, W.M.** *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **82**: 398–402 (1988).
9. **Pang, L.W. et al.** *Bulletin of the World Health Organization*, **67**: 51–58 (1989).
10. **Karwacki, J.J. et al.** *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **84**: 55–57 (1990).
11. **Phillips-Howard, P.A. & West, L.** *Journal of the Royal Society of Medicine*, **83**: 82–85 (1990).
12. **Nordenwall, B. et al.** *Scandinavian journal of gastroenterology*, **20**: 783–790 (1985).
13. **Mobacken, H. et al.** *Acta dermato-venereologica*, **64**: 400–404 (1984).
14. **Mann, R.** *Adverse drug reactions: the scale and nature of the problem and the way forward.* Carnforth, New Jersey, Partenon Publishing, 1987.
15. **Hellgren, U. et al.** *British medical journal*, **295**: 365–366 (1987).
16. **Phillips-Howard, P.A. et al.** *Lancet*, **2**: 803–804 (1989).
17. **Ström, J.** *Acta medica Scandinavica*, **201**: 131–136 (1977).
18. **Gordin, F.M. et al.** *Annals of internal medicine*, **100**: 495–499 (1984).
19. **Wharton, J.M. et al.** *Annals of internal medicine*, **105**: 37–44 (1986).
20. **Fredriks, D.A. & Mowers, R.M.** *Drug intelligence and clinical pharmacy*, **22**: 899–900 (1988).
21. **Putterman, C. et al.** *Lancet*, **2**: 52 (1990).
22. **Arnold, P.A. et al.** *Drug intelligence and clinical pharmacy*, **22**: 43–44 (1988).
23. **Böttiger, L.E. et al.** *Acta medica Scandinavica*, **205**: 457–461 (1979).
24. **Kelly, J.P. et al.** *Archives of internal medicine*, **149**: 1036–1040 (1989).
25. **Guillaume, J.C. et al.** *Archives of dermatology*, **123**: 1166–1170 (1987).
26. **Ward, S.A. et al.** *British journal of clinical pharmacology*, **27**: 781–787 (1989).